UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

HEALTH INSURANCE PLAN OF NEW YORK, on behalf of itself and all others similarly situated, Plaintiff, v AVENTIS PHARMACEUTICALS, INC. Defendant.	Civil Action No. 07-cv-6785 (HB) **ECF CASE**

FIRST AMENDED CLASS ACTION COMPLAINT

Health Insurance Plan of New York ("Plaintiff") brings this class action on behalf of itself and classes of End-Payors, as defined below, as to the liability issues sought herein, against Aventis Pharmaceuticals, Inc. ("Defendant" or "Aventis"), for violations of federal and state antitrust laws, state consumer protection laws and state common law principles of unjust enrichment. Plaintiff makes its allegations upon personal knowledge as to matters relating to itself and upon the investigation of its counsel and information and belief as to all other matters.

NATURE OF THE ACTION

1. This litigation arises from a series of actions undertaken by Defendant to unlawfully maintain its monopoly on the brand-name drug Arava. Faced with the threat of losing market exclusivity, Defendant engaged in a series of anticompetitive and unlawful actions that ultimately extended exclusivity of the sale of its brand name prescription drug Arava.

2. This is a nationwide class action brought under federal antitrust laws, and a multi-state class action brought under state antitrust laws, state consumer protection laws, and state

common law seeking damages, restitution and declaratory and injunctive relief arising from the manufacture and marketing of Arava, a drug used in the treatment of rheumatoid arthritis. Defendant's unlawful, unjust and anticompetitive conduct arising from the abuse of the citizens petition process under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") delayed generic versions of Arava from entering the United States market, thereby causing injury to Plaintiff and members of the End-Payor Classes as defined at Paragraphs 80-81 below.

3. Arava (leflunomide) is a pyridimine synthesis inhibitor. The generic name for Arava is leflunomide. It is used to reduce the signs and symptoms of active rheumatoid arthritis in adults, retard the damage to effected joints, and improve physical function.

4. One September 10, 1998, the United States Food and Drug Administration approved Arava for sale by Defendant in the United States by the Food and Drug Administration ("FDA") in strengths of 10mg, 20mg and 100mg.

5. Although Defendant held no relevant patent protection on the formula for Arava, as the filer of a New Drug Application ("NDA"), Defendant enjoyed a statutory exclusive right to market Arava in the United States in all three dosage forms until March 10, 2004.

6. On or about March 10, 2004, several generic manufacturers, including Kali Laboratories, Barr Laboratories, TEVA Pharmaceuticals, Apotex Corp., and Sandoz, Inc. filed Abbreviated New Drug Applications ("ANDAs") with the FDA seeking approval to market a generic version of Arava in the 10mg and 20mg strengths. Pursuant to applicable regulations, generic manufacturers were required to wait until this date to file an ANDA.

7. On March 31, 2005, more than a year after the various generic manufacturers filed their ANDAs, and on the eve of approval by the FDA of various generic forms of Arava,

Defendant filed a citizens petition with the FDA pursuant to 505(j) of the FDCA in an attempt to delay generic versions of Arava from entering the United States market.

8. Defendant's citizen petition was without merit, raised no legitimate concerns about the generic version of Arava at issue, and was submitted not to influence FDA policy or procedure, but merely to delay the FDA approval of generic Arava and extend Defendant's monopoly for Arava products in the United States.

9. Defendant's citizen petition had the desired effect. As a result of Defendant's citizen petition, the availability of generic Arava in the United States was delayed at least five months. Defendants sold in excess of $200 million worth of Arava in the last year of brand name exclusivity.

10. As a direct and proximate result of Defendant's unlawful conduct, End-Payors were denied the benefits of free and unrestrained competition in the market for Arava and its generic equivalent. More specifically, Plaintiff and members of the End-Payor Classes were denied the opportunity to choose between the brand name prescription drug and lower priced generic versions and were thereby forced to pay supracompetitive prices.

11. In Count I of this Complaint, Plaintiff, on behalf of itself and all others who are members of the Nationwide Class as herein defined, seek equitable, injunctive and declaratory relief against Defendant based on allegations of monopolization of, and an attempt to monopolize, the market for Arava and its generic equivalents, in violation of Section 2 of the Sherman Act, 15 U.S.C. § 2.

12. Count II is brought by Plaintiff on behalf of itself and all other members of the Statewide Classes who purchased or paid for Arava and its generic bio-equivalents in Alaska,

Arizona, Arkansas, California, Colorado, Connecticut, Delaware, the District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, and Wisconsin. Count II is brought pursuant to state antitrust and unfair and deceptive trade practices acts.

13. Count III is brought by Plaintiff on its own behalf and on behalf of the End-Payor Classes, seeking a constructive trust and disgorgement of the unjust enrichment of Defendant.

PARTIES

14. Plaintiff, The Health Insurance Plan of New York ("Plaintiff" or "HIPNY"), is a New York corporation with its principal place of business at 55 Water Street, New York, New York. HIPNY provides prescription benefits coverage to its members, who reside throughout the United States and Puerto Rico. During the period April 1, 2005 to September 13, 2005, HIPNY paid United States pharmacies more than $137,000 to purchase Arava for use by its members.

15. Defendant, Aventis Pharmaceuticals, Inc., is a Delaware corporation with its principal place of business located in Bridgewater, New Jersey.

JURISDICTION AND VENUE

16. This action is brought under Section 16 of the Clayton Act, 15 U.S.C. § 26, for injunctive and equitable relief to remedy Defendant's violations of the federal antitrust laws, particularly Section 2 of the Sherman Antitrust Act, 15 U.S.C. § 2. The Court has jurisdiction over this action pursuant to 28 U.S.C. §§ 1331 and 1337(a) and 15 U.S.C. § 26. In addition, this

Court has jurisdiction over the state law claims pursuant to 28 U.S.C. § 1332(d), as amended in 2005, and 28 U.S.C. § 1367.

17. Venue is proper in this judicial district pursuant to 15 U.S.C. § 22 and 28 U.S.C. §§ 1391(b) and (c), 28 U.S.C. § 1407 and 15 U.S.C. § 22 because Defendant does business in this judicial district.

18. The illegal monopolization and attempt to monopolize the market for Arava and generic versions of Arava, as alleged herein, have substantially affected interstate and foreign commerce.

INTERSTATE TRADE AND COMMERCE

19. Defendant's efforts to monopolize and restrain competition in the market for Arava alleged herein have substantially affected interstate and foreign commerce.

20. During all or part of the Class Period, Defendant manufactured and sold substantial amounts of Arava in a continuous and uninterrupted flow of commerce across state lines and throughout the United States. Defendant maintained an exclusive license to market and sell Arava in the United States during the Class Period, as herein defined.

21. At all material times, Defendant manufactured and sold Arava and shipped it across state lines and sold Arava to customers located outside its state of manufacture.

22. During all or part of the Class Period, as herein defined, Defendant transmitted funds as well as contracts, invoices and other forms of business communications and transactions in a continuous and uninterrupted flow of commerce across state and national lines in connection with the sale of Arava.

23. In furtherance of its efforts to monopolize and/or restrain competition in the market for Arava and its generic equivalents, Defendant employed the United States mails and interstate and international telephone lines, as well as means of interstate and international travel.

RELEVANT MARKET AND MARKET POWER

24. During the Class Period, the relevant antitrust product market is the manufacture and sale of Arava and its generic equivalent leflunomide. Other treatments for rheumatoid arthritis are not legally or otherwise substitutable for Arava, both by virtue of FDA approval requirements and by virtue of the unique qualities of the drug. Shortly after the launch of Arava, Defendant claimed that "the treatments we have now [for rheumatoid arthritis] are good but many patients have an incomplete response or don't have a response and need a choice such as Arava." The relevant geographic antitrust market for Arava is the United States.

25. During the Class Period, Defendant's share of the relevant market was 100%, and Defendant maintained monopoly power in the relevant market during that time period.

MARKET EFFECTS

26. The acts and practices of Defendant, as herein alleged, had the purpose and effect of restraining competition unreasonably and injuring competition by protecting Arava from generic competition in the relevant market.

27. If generic competitors had been able to enter the relevant market and compete with Defendant, End-Payors such as Plaintiff would have been free to substitute a lower-priced generic for the higher-priced brand name drug and Plaintiffs and the members of the classes would have paid less for leflunomide. Pharmacists are permitted, and in some instances are required by law, to substitute generic drugs for their branded counterparts, unless the prescribing

physician has directed that the branded product be dispensed. In addition, there is a ready market for generic products because certain End-Payors of prescription drugs (e.g., managed care plans) encourage or insist on the use of generic drugs whenever possible. A generic product can quickly and efficiently enter the marketplace at substantial discounts, generally leading to a significant erosion of the branded drug's sales within the first year.

28. By preventing generic competitors from entering the market, Defendant injured Plaintiff and the other members of the classes in their business or property by causing them to pay more for leflunomide than they otherwise would have paid. Defendant's unlawful conduct deprived Plaintiff and other End-Payors of the benefits of competition that the antitrust laws and applicable state consumer protection laws were designed to preserve.

FACTUAL ALLEGATIONS

A. Federal Regulation of Prescription Drugs

1. Brand-Name Drugs v. Generic Drugs

29. The laws governing pharmaceutical products are meant to balance the competing policy goals of providing new drug inventors an economic return on their investment while also ensuring consumers access to additional and more affordable generic versions of brand name drugs.

30. The manufacture, marketing, distribution and sale of prescription drugs is one of the most profitable industries in the United States. The U.S. market accounts for more than 40% of the world's prescription pharmaceutical revenues. The cost of prescription drugs in the United States has been rising at double digit rates for years and the cost of drugs dispensed in the United States in 2005, both name brand and generic, exceeded $250 billion.

31. The availability of generic drugs has been one of the most effective means of lowering the cost of prescription drugs. Generic drugs, which also must be approved by the FDA, have the same active chemical composition and provide the same therapeutic effects as the pioneer brand-name drugs upon which they are modeled. The FDA will assign an "AB" rating to generic drugs that the FDA determines are bioequivalent to pioneer or brand-name drugs.

32. To be deemed a bioequivalent drug and assigned an "AB" rating by the FDA, a generic version of a pioneer drug must contain the same active ingredient(s), dosage form, route of administration and strength as the brand name drug. If it meets the FDA requirements for bioequivalence, the generic drug can be substituted (and in some instances must be substituted) for the pioneer or brand-name drug at the pharmacy counter without further intervention by a physician.

33. Generic drugs are generally priced substantially below the brand-name drugs to which they are bioequivalent. A 1998 study conducted by the Congressional Budget Office (the "CBO") concluded that generic drugs save consumers and third-party payors between $8 billion and $10 billion a year. A report prepared by the Government Accounting Office in August 2000 observed, "Because generic drugs are not patented and can be copied by different manufacturers, they often face intense competition, which usually results in much lower prices than brand-name drugs."

34. The Federal Trade Commission ("FTC") estimates that the first generic manufacturer to enter the market typically charges between 70% and 80% of the price of the brand-name drug. In a report from the staff of Bureau of Competition and of Policy Planning of the FTC have noted " . . . the more generic versions of the same drug product that are on the

market, the closer the price is to its competitive level, regardless of which generic companies are marketing the drug product."

35. A brand-name drug loses a significant portion of its market share to generic competitors soon after the introduction of generic competition, even if the brand-name manufacturer lowers prices to meet competition.

2. Prescriptions for Generic Drugs

36. If a generic version of a brand-name drug exists and the physician has not specifically indicated on the prescription "DAW" or "dispense as written" (or similar indications, the wording of which varies slightly from state to state), then: (a) for consumers covered by most insurance plans, the pharmacist will substitute the generic drug; (b) for consumers whose purchases are not covered by insurance plans, the pharmacist will offer the consumer the choice of purchasing the branded drug, or the AB-rated generic at a lower price and (c) many state laws require a pharmacist to fill a prescription with an available generic formulation of the drug.

37. Once a physician writes a prescription for a brand-name drug such as Arava, that prescription defines and limits the market to the drug named or its AB-rated generic equivalent. Only drugs which carry the FDA's AB generic rating may be substituted by a pharmacist for a physician's prescription for a brand-name drug.

3. New Drug Applications (NDAs)

38. The statute regulating the manufacture and distribution of drugs and medical devices in the United States is the FDCA.

39. Under the FDCA, approval by the FDA, the governmental body charged with regulation of the pharmaceutical industry, is required before a company may begin selling a new

drug in interstate commerce in the United States. 21 U.S.C. § 355(a). Pre-market approval for a new drug must be sought by filing an NDA with the FDA under § 355(b) of the FDCA demonstrating that the drug is safe and effective for its intended use.

40. Once the safety and effectiveness of a new drug is approved by the FDA, it may be used in the United States only under the direction and care of a doctor who writes a prescription specifying the drug, which must be purchased from a licensed pharmacist. Generally, the pharmacist must, in turn, fill the prescription with the drug specified by the physician unless a generic version is available that has been approved by the FDA for substitution as bioequivalent.

4. Abbreviated New Drug Applications ("ANDAs") For Generic Drugs

41. Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. § 355 ("Hatch-Waxman Act") to establish an abbreviated process to expedite and facilitate the development and approval of generic drugs. Consumers benefit from the choice and competition. To effectuate its purpose, the Hatch-Waxman Act permits a generic drug manufacturer to file an Abbreviated New Drug Application ("ANDA"), which incorporates by reference the safety and effectiveness data developed and previously submitted by the manufacturer of the original, pioneer drug.

42. If no patent covers the formula for a particular drug for which an NDA has been approved by the FDA, 21 U.S.C. § 355 (j)(5)(F)(ii) provides that no ANDA may be submitted with respect to that formulation for a period of five years, effectively providing a five year period of market exclusivity to the holder of the NDA from the date of FDA approval. In addition, pursuant to § 505A of the FDCA, if a named brand manufacturer meets certain criteria with

respect to testing for the pediatric use of the product, the five year exclusivity period is extended by 6 months.

5. Citizens Petitions to the FDA

43. 21 C.F.R. § 10.30 provides for a formal mechanism by which a person may file a petition with the FDA requesting, among other things, that the agency take, or refrain from taking, any form of administrative action. These requests are commonly referred to as citizen petitions.

44. Citizens petitions provide an opportunity for individuals to express their genuine concerns about safety, scientific, or legal issues regarding a product anytime before, or after, its market entry.

45. Other than the form of such citizen petition, set forth in 21 C.F.R. § 10.30, there are no restrictions on the subject matter of a citizen petition.

46. 21 C.F.R. § 10.30(e)(2) provides that the FDA Commissioner shall respond to each citizens petition within 180 days of receipt. That response may be to approve the request, approve it in part, deny the request or to provide a tentative response with an estimate on a time for a full response.

47. Reviewing and responding to these petitions is often a resource-intensive and time consuming task because the FDA must research the petition's subject, examine scientific, medical, legal and sometimes economic issues, coordinate internal agency review and clearance of the petition response.

6. Use of Citizens Petitions by Named Brand Drug Manufacturers As a Mechanism to Forestall Generic Competition

48. In recent years the citizen petition process has been subject to misuse by some brand name pharmaceutical manufacturers as a tactic not to raise legitimate concerns about the safety or efficacy of generic products but instead to extend their name brand monopoly. These citizen petitions are often filed on the eve of FDA approval of an ANDA, an ANDA that may have been pending for a year or more, and have the effect of delaying the entry of the generic product for an additional period from a few months to over a year while the FDA evaluates and responds to the citizen petition.

49. To delay competition may be a lucrative strategy for an incumbent manufacturer. The cost of filing an improper citizen petition may be trivial compared to the value of securing even a few months delay in a rival's entry into the market.

50. FDA officials have acknowledged ongoing abuses of the citizen petition process. FDA Chief Counsel Sheldon Bradshaw noted that in his time at the agency he had "seen several examples of citizen petitions that appear designed not to raise timely concerns with respect to the legality or scientific soundness of approving a drug application but rather to try to delay the approval simply by compelling the agency to take the time to consider arguments raised in the petition whatever their merits and regardless of whether or not the petitioner could have made those very arguments months and months before."

51. In July 2006, Gary Buehler, R. Ph., Director of the Office of Generic Drugs Center for Drug Evaluation and Research ("CDER") at the FDA, noted that of 42 citizens petitions raising issues about the approvability of generic products "very few . . . have presented

data or analysis that significantly altered FDA's policies." Of these 42, only three petitions led to a change in the FDA's policy on the basis of data or information submitted in the petition.

52. While there is no statutory requirement that the FDA withhold approval of an ANDA while a citizen petition is pending, it is the practice of the FDA, well known in the pharmaceutical industry, to consider and respond to a citizen petition prior to approval of an ANDA. On this subject Mr. Buehler acknowledged, "[i]t is very rare that petitions present new issues that CDER has not fully considered, but the Agency must nevertheless assure itself of that fact by reviewing the citizen petitions."

B. Defendants' Unlawful Scheme to Forestall Generic Competition for Arava

53. Arava was approved for sale by Defendant in the United States by the FDA on September 10, 1998 in strengths of 10mg, 20mg and 100mg. The usual daily dose of Arava is 20mg. The 10mg dosage is used in patients who do not tolerate the 20mg dose adequately.

54. Because of the long half-life of the active ingredient in Arava, the use of a "loading dose" of 100mg per day for three days is recommended in Arava's approved labeling. The use of the loading dose is not essential to the effective use of the product, and elimination of the loading dose may actually decrease the risk of adverse events for some patients.

55. As the filer of an NDA for Arava, Defendant enjoyed the exclusive right to market Arava in all three dosage forms for five years pursuant to section 505(j)(5)(F)(ii) of the FDCA. In addition, because the FDA determined under section 505A of the FDCA that Arava was entitled to pediatric exclusivity, the period of exclusive marketing of Arava by Defendant was extended 6 months. Defendant's exclusive right to market Arava ended on March 10, 2004.

56. Defendant devised a strategy to attempt to forestall entry of generic manufacturers into the market for 10mg and 20mg tablets. In September 2002, four years after obtaining FDA approval, Defendant stopped selling the 100mg loading dose of Arava. Instead, Defendant began providing the loading dose as a free sample to physicians in the form of a blister pack containing three 100mg tablets of Arava.

57. Defendant stopped selling the 100mg tablets in anticipation of the loss of market exclusivity as a means of forestalling generic entry into the more lucrative 10mg and 20mg markets. This was attempted by promoting the use of named brand Arava by physicians provided the free loading dose and by disincentivizing any generic manufacturer from sponsoring an ANDA with respect to the 100mg tablet, as it is made available free to physicians through Defendant. Defendant would later attempt to use the lack of any ANDA for the 100mg tablet to argue that any ANDA for the 10mg and 20mg dosages must be denied unless accompanied by an ANDA for the 100mg dosage or unless the ANDA met additional bioequivalence tests that are not required by federal regulation.

58. Pursuant to § 505(c)(3)(E)(ii) of the FDCA, no ANDA could be submitted until the expiration of Defendant's exclusivity period for Arava on March 10, 2004.

59. On or about March 10, 2004 several generic manufacturers, including Kali Laboratories, Barr Laboratories, TEVA Pharmaceuticals, Apotex Corp., and Sandoz, Inc. filed ANDAs with the FDA seeking approval to market a generic version of Arava in the 10mg and 20mg strengths.

60. The approval process for ANDAs can be lengthy as the FDA has a "first in, first reviewed" policy with respect to ANDAs.

61. On March 31, 2005, more than a year after the various generic manufacturers filed ANDAs seeking approval to enter the market, Defendant filed a citizen petition with the FDA, pursuant to §505(j) of the FDCA, in an attempt to delay generic versions of Arava from entering the United States market. A copy of that citizen petition is attached hereto as Exhibit A.

62. Defendant's citizen petition urged the FDA to withhold approval of any ANDA that did not seek approval of a 100mg leflunomide tablet that is bioequivalent to Defendant's Arava 100mg tablets or did not establish *in vivo* bioequivalence between five 20mg leflunomide tablets and one Arava 100mg tablet.

63. Defendant's citizen petition was filed on the eve of the FDA's approval of the various ANDAs for generic leflunomide using arguments and citations that were known and available to Defendant well before they were submitted to the FDA in Defendant's citizen petition. The FDA's response to the citizen petition, issued on September 13, 2005, notes that Defendant's petition was submitted approximately one year after the end of the extended exclusivity period for brand name Arava - March 10, 2004. One commenter notes "that this would be at the end of the normal ANDA review cycle for an ANDA submitted on or near the date ANDAs were first eligible for submission, suggesting that the Petition intends (at least in part) to delay generic competition. We also note that the majority of the citations in your Petition are many years old, and were available to Aventis well before the petition was submitted." A copy of the FDA's response to Defendant's citizen petition is attached hereto as Exhibit B.

64. Defendant's petition argued that because no ANDA had been submitted for the 100mg loading dose and because the FDA had previously required, in the process of evaluating Defendant's NDA, that if Defendants wished to obtain approval for the use of five 20mg tablets

as the "loading dose" Defendant must provide evidence of bioequivalence between five 20mg tablets of branded Arava and the 100mg strength, that any ANDA applicant must also provide evidence of bioequivalence of five of its 20 mg generic tablets with the 100mg branded Arava tablet or submit an ANDA for a 100mg strength generic tablet.

65. Defendant argued that any label on the generic 10mg or 20mg tablets for which the generic manufacturer did not also manufacture a 100mg loading dose would need to omit any mention of a loading dose and would therefore render the generic formulations "less effective" than named brand Arava and therefore not capable of approval under applicable FDA labeling regulations.

66. Defendant's citizen petition ignored the fact that the FTCA and bioequivalence regulations do not require that an ANDA sponsor demonstrate equivalence between different strengths of its own product line, only that it demonstrate bioequivalence between the dosage of the drug which is the subject of the ANDA and the named brand drug of the same dosage. 21 C.F.R. Part 320.

67. As the FDA response points out, the fact that generic manufacturers only sought to market the 10mg and 20mg did not necessitate that they omit any mention of a loading dose for leflunomide in their labeling. The FDA stated that "[Defendants] seem to ignore a third possibility: that the labeling for a generic leflunomide product can recommend a loading dose of 3 x 100 mg that can be accomplished by the use of an approved 100 mg tablet from a different manufacturer. Given the unusual manner in which the 100 mg tablet for the loading dose has been distributed by Aventis (i.e. in blister packs of 3, for free and only to, and at the request of, a physician) and the fact that there are circumstances when a loading dose should perhaps not be

used, we do not find it unreasonable for a generic manufacturer to elect to market only the other dosage strengths."

68. Defendant's citizen petition was objectively baseless and was submitted for the purpose not of influencing FDA policy or addressing any legitimate concern about the efficacy or safety of generic leflunomide, but to forestall generic competition in the United States market for Arava products during the time it would take the FDA to evaluate and respond to the citizen petition.

69. On September 13, 2005, the same date on which the FDA denied Defendant's citizen petition, the FDA granted final approval to the ANDAs sponsored by Kali Laboratories, Barr Laboratories, TEVA Pharmaceuticals, Apotex Corp., and Sandoz, Inc for the 10 mg and 20 mg dosage tablets of leflunomide. These generic manufacturers, as well as Prasco Laboratories, under an agreement with Defendant to sell an "authorized generic" version leflunomide, began selling generic Arava in the United States market on September 14, 2005.

70. Had Defendant not filed its frivolous citizens petition, the FDA would have approved the generic versions of Arava on or about March 2005 and the generic manufacturers would have immediately began selling substantially cheaper dosages of leflunomide at that time.

71. As a direct and proximate result of Defendant's unlawful conduct, consumers were denied the benefits of free and unrestrained competition in the market for Arava and its generic equivalent from March 31, 2005, the date of the Defendant's citizen petition, until September 14, 2005, the date when generic leflunomide became available in the United States. More specifically, Plaintiff and members of the Class were denied the opportunity to choose

between the brand name prescription drug and lower priced generic versions and were thereby forced to pay supracompetitive prices for leflunomide.

72. Through the anticompetitive conduct alleged herein, Defendant was able to charge supracompetitive prices for leflunomide, and thus, by definition, maintained monopoly power with respect to leflunomide sold in the United States. To the extent that Plaintiff is legally required to prove monopoly power circumstantially by first defining a relevant product market, Plaintiff alleges that the relevant product market is all leflunomide products, *i.e.,* Arava (in all its forms and dosage strengths), and bioequivalent leflunomide products. For the entire period relevant to this case, Defendant was able to profitably maintain the price of its branded leflunomide products well above competitive levels.

73. Defendant's market share in the relevant market at all times during the relevant time period was 100%.

74. Defendant's actions are part of, and in furtherance of, the illegal monopolization alleged herein, were authorized, ordered or done by Defendant's officers, agents, employees or representatives while actively engaged in the management of Defendant's affairs.

75. Defendant's illegal acts to delay the introduction and/or dissemination into the U.S. marketplace of any generic version of Arava resulted in Plaintiff paying more than it would have paid for leflunomide, absent Defendant's illegal conduct.

C. Effects on Competition and Damages to Plaintiff and Class

76. Defendant's exclusionary conduct has delayed or prevented the sale of generic leflunomide in the United States, and unlawfully enabled Defendant to sell Arava at artificially inflated prices. But for Defendant's illegal conduct, generic competitors, as well as Prasco

Laboratories who had an agreement with Defendants to market an "authorized generic" version of leflunomide as soon as any generic version of leflunomide was approved by the FDA, would have been able to successfully market generic versions of Arava capsules by March 31, 2005.

77. Defendant's scheme meant to delay generic entry is exclusionary and unreasonably restrains competition.

78. If manufacturers of generic leflunomide had been able to enter the marketplace and effectively compete with Defendant earlier, as set forth above, Plaintiff and other members of the classes would have substituted lower priced generic leflunomide for the higher priced brand name Arava for some or all of their leflunomide requirements, and/or would have received discounts on some or all of their remaining Arava purchases.

CLASS ACTION ALLEGATIONS

79. Plaintiff brings this action pursuant to Rule 23 of the Federal Rules of Civil Procedure, specifically, Rules 23(b)(2), 23(b)(3) and 23(c)(4) for liability issues only, on behalf of the following classes:

a. a Nationwide Class under federal antitrust laws seeking declaratory and injunctive relief on behalf of:

> All persons or entities throughout the United States and its territories who purchased and/or paid for Arava or generic versions of Arava during the period March 31, 2005 to September 14, 2005 ("the Class Period") for consumption by themselves, their families, or their members, employees, insureds, participants or beneficiaries (the "Nationwide Class"). For purposes of the Nationwide Class definition, persons and entities "purchased" Arava if they paid some or all of the purchase price.

b. a Multistate Class under state antitrust and/or consumer protection statutes and state common law of unjust enrichment on behalf of:

> All persons or entities in the following states: Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, the District of Columbia, Florida, Georgia, Hawaii, Idaho, Illinois, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, and Wisconsin who purchased and/or paid for Arava or generic versions of Arava during the period March 31, 2005 to September 14, 2005 ("the Class Period") for consumption by themselves, their families, or their members, employees, insureds, participants or beneficiaries (the "Multistate Class"). For purposes of the Multistate Class definition, persons and entities "purchased" Arava if they paid some or all of the purchase price.

80. Collectively, the Nationwide Class and the Multistate Class are referred to herein as the End-Payor Classes. Excluded from the End-Payor Classes are Defendant, its officers, subsidiaries and affiliates; all government entities (except for government-funded employee benefit plans); all persons or entities that purchased Arava for purposes of resale, or directly from Defendant or its affiliates; and the judge in this case and any members of his/her immediate family.

81. Plaintiff seeks class certification pursuant to Rule 23(b)(2) of the Federal Rules of Civil Procedure as to declaratory and equitable relief sought herein, and Rule 23(b)(3) and 23(c)(4) as to liability issues sought herein. Plaintiff does not seek to certify a class for purposes of issues of damages.

82. Although Plaintiff does not know the exact number of class members, they believe it to be, at a minimum, in the tens of thousands. In its last year of market exclusivity

Arava had annual U.S. sales in excess of $200 million. Thus, members of the End-Payor Classes are numerous and joinder is impracticable. The Class members are identifiable, *inter alia*, from information and records that are required by law to be maintained by pharmacies, drugstores, pharmaceutical benefits managers, and managed care organizations.

83. Questions of law and fact common to the members of the Class predominate over questions, if any, that may affect only individual members, in part because Defendant has acted and refused to act on grounds generally applicable to the End-Payor Classes, thereby making appropriate equitable, injunctive and declaratory relief with respect to the End-Payor Classes as a whole. Such conduct includes the Defendant's exclusionary and anti-competitive efforts (i) in filing a baseless citizens petition with the FDA for the sole purpose of delaying the FDA's approval of generic competition and (ii) converting the relevant market from one confronted with generic competition to one that is not for the sole purpose of monopolizing and attempting to monopolize the market for Avara.

84. Questions of law and fact common to the End-Payor Classes include:

a. whether Defendant maintained or attempted to maintain monopoly power by delaying generic entry;

b. whether direct proof of Defendant's monopoly power is available, and if available, whether it is sufficient to prove Defendant's monopoly power without the need to also define a relevant market;

c. To the extent a relevant market or markets must be defined, what that definition is or those definitions are;

d. whether the activities of Defendant as alleged herein have substantially affected interstate commerce;

e. whether Defendant's filing of a citizens petition with respect to approval of an ANDA with respect to leflunomide described herein was baseless;

f. whether Defendant filed the citizens petition described herein for the purpose of preventing competition;

g. Whether Defendant intentionally and unlawfully excluded competitors and potential competitors from the market for Arava and generic bio-equivalents to Arava;

h. whether Plaintiff and members of the End-Payor Classes are entitled to declaratory, equitable and/or injunctive relief; and

i. whether the complained of conduct of the defendant violates federal and state antitrust, trade practices acts and common law.

85. Plaintiff's claims are typical of the members of the End-Payor Classes, in that Plaintiff purchased and/or paid for Arava during the Class Period.

86. Plaintiff will fairly and adequately protect and represent the interests of the End-Payor Classes. The interests of the Plaintiff are not antagonistic to those of the End-Payor Classes. In addition, the Plaintiff is represented by counsel who are experienced and competent in the prosecution of complex class action antitrust litigation.

87. Class action treatment is a superior method for the fair and efficient adjudication of the controversy, in that, among other things, such treatment will permit a large number of similarly situated persons to prosecute the liability aspects of their common claims in a single forum simultaneously, efficiently, and without the unnecessary duplication of evidence, effort,

and expense that numerous individual actions would engender. The benefits of proceeding through the class mechanism, including providing injured persons or entities with a method for establishing whether the conduct complained of herein violates federal and state antitrust, trade practices acts and common law, substantially outweigh any difficulties that may arise in management of this class action.

88. Plaintiff knows of no difficulty to be encountered by litigating this action that would preclude its maintenance as a class action.

FIRST CAUSE OF ACTION

FOR DECLARATORY AND INJUNCTIVE RELIEF UNDER SECTION 16 OF THE CLAYTON ACT FOR DEFENDANTS' VIOLATIONS OF SECTION 2 OF THE SHERMAN ACT

89. Plaintiff repeats and realleges the preceding and subsequent paragraphs as though set forth herein.

90. As described above, Defendant knowingly and willfully engaged in a course of conduct designated to improperly obtain and extend its monopoly power. This course of conduct included, *inter alia*, (i) filing a baseless citizens petition with the FDA for the sole purpose of delaying the FDA's approval of generic competition, and (ii) the intentional conversion of the relevant market from one confronting generic competition to one that is not. The result of Defendant's unlawful conduct was to illegally extend its monopoly.

91. Defendant intentionally and wrongfully created and maintained a monopoly power in violation of Section 2 of the Sherman Act, 15 U.S.C. § 2.

92. Plaintiff and the other members of the End-Payor Classes have been injured in their business or property by reason of Defendant's antitrust violation alleged herein. Their

injury consists of being deprived of the ability to purchase less expensive, generic versions of Arava, and paying higher prices for such products than they would have paid in the absence of the antitrust violation. The injury to Plaintiff and the End-Payor Classes is the type of injury antitrust laws were designed to prevent, and the injury flows from Defendant's unlawful conduct.

93. Plaintiff and the End Payor Classes, pursuant to Rule 57 of the Federal Rules of Civil Procedure and 18 U.S.C. § 2201(a), hereby seek a declaratory judgment that Defendant's conduct in seeking to prevent competition as described herein violates Section 2 of the Sherman Act.

94. Plaintiff and the End-Payor Classes further seek equitable and injunctive relief pursuant to Section 16 of the Clayton Act, 15 U.S.C. § 26, and other applicable law, to correct for the anticompetitive market effects caused by the unlawful conduct of Defendant and other relief so as to assure that similar anticompetitive conduct does not occur in the future.

SECOND CAUSE OF ACTION

FOR COMPENSATORY AND EXEMPLARY DAMAGES, INJUNCTIVE AND DECLARATORY RELIEF UNDER THE ANTITRUST AND/OR CONSUMER PROTECTION STATUTES OF THE INDIRECT PURCHASER STATES

95. Plaintiff repeats and realleges the preceding and subsequent paragraphs as though set forth herein.

96. Defendant's conduct described herein constitutes unlawful acts of monopolization and attempts to monopolize, as well as prohibited practices and unconscionable conduct under the antitrust and/or unfair and deceptive trade practices acts of the following states:

a. Alaska: The aforementioned practices by Defendant were and are in violation of the Alaska Stat. § 45.50.471, *et seq.*;

b. Arizona: The aforementioned practices by Defendant were and are in violation of the Arizona Uniform State Antitrust Act, Ariz. Rev. Stat. § 44-1401, *et seq.*, the Arizona Consumer Fraud Act, Ariz. Rev. Stat. § 44-1521, *et seq.*, and the Constitution of the State of Arizona, Article 14, §15;

c. Arkansas: The aforementioned practices by Defendant were and are in violation of the Ark. Code § 4-88-101, *et seq.*;

d. California: The aforementioned practices by Defendant were and are in violation of the Cal. Bus. & Prof. Code §§ 16700, *et seq.*, and Cal. Bus. & Prof Code §§ 17200, *et seq.*;

e. Colorado: The aforementioned practices by Defendant were and are in violation of the Colo. Rev. Stat. § 61-105, *et seq.*;

f. Connecticut: The aforementioned practices by Defendant were and are in violation of the Conn. Gen. Stat § 42-110b, *et seq.*;

g. Delaware: The aforementioned practices by Defendant were and are in violation of the 6 Del. Code § 2511, *et seq.*;

h. District of Columbia: The aforementioned practices by Defendant were and are in violation of the District of Columbia Antitrust Act, D.C. Code § 28-45031, *et seq.*, and D.C. Code § 28-3901;

i. Florida: The aforementioned practices by Defendant were and are in violation of the Florida Antitrust Act, Fla. Stat. Ann. § 542.15, *et seq.*, and the Florida Deceptive and Unfair Trade Practices Act, Fla. Stat. Ann. § 501 Part II, and § 501.201, *et seq.*;

j. Georgia: The aforementioned practices by Defendant were and are in violation of the Ga. Stat. § 10-1-392, *et seq.*;

k. Hawaii: The aforementioned practices by Defendant were and are in violation of Hawaii Revised Statues §§ 480-2, 480-3, and 480-4;

l. Idaho: The aforementioned practices by Defendant were and are in violation of the Idaho Code § 48-601, *et seq.*;

m. Illinois: The aforementioned practices by Defendant were and are in violation of the 815 ILCS § 505/1, *et seq.*;

n. Iowa: The aforementioned practices by Defendant were and are in violation of the Iowa Competition Law, Iowa Code §§ 553.4, 553.5 (1997);

o. Kansas: The aforementioned practices by Defendant were and are in violation of the Kansas Monopolies and Unfair Trade Act, Kan. Stat. Ann. § 50-101, *et seq.*, and the Kansas Consumer Protection Act, Kan. Stat. Ann § 50-623, *et seq.*;

p. Kentucky: The aforementioned practices by Defendant were and are in violation of the Kentucky Consumer Protection Act, Ky. Rev. Stat. Ann. § 367.110, *et seq.*, and the Kentucky Unfair Trade Practices Act, Ky. Rev. Stat. Ann § 365.020, *et seq.*;

q. Louisiana: The aforementioned practices by Defendant were and are in violation of the Louisiana Monopolies Law, La. Rev. Stat. Ann. § 51:121 and § 51:137 *et seq.*,

and the Louisiana Unfair Trade Practices and Consumer Protection Law, La. Rev. Stat. Ann. § 51:1401, *et seq.*;

r. Maine: The aforementioned practices by Defendant were and are in violation of the Me. Rev. Stat. Ann. 10, § 1101, *et seq.*, and 5 Me. Rev. Stat. § 207, *et seq.*;

s. Maryland: The aforementioned practices by Defendant were and are in violation of the Md. Com. Law Code § 13-101, *et seq.*;

t. Massachusetts: The aforementioned practices by Defendant were and are in violation of the Mass. Ann. Laws ch. 93, *et seq.*, and Mass. Gen. L. Ch. 93A, *et seq.*;

u. Michigan: The aforementioned practices by Defendant were and are in violation of the Michigan Antitrust Reform Act, Mich. Comp. Laws §445.771, *et seq.*, and the Michigan Consumer Protection Act, § 445.901, *et seq.*;

v. Minnesota: The aforementioned practices by Defendant were and are in violation of the Minnesota Antitrust Law of 1971, Minn. Stat. § 325D.49, and § 325D-52 *et seq.*, and the Minnesota Consumer Fraud Act, Minn. Stat § 325F.67, *et seq.*; and Minn. Stat. § 8.31, *et seq.*;

w. Mississippi: The aforementioned practices by Defendant were and are in violation of the Miss. Code Ann. § 75-21-1, *et seq.*;

x. Missouri: The aforementioned practices by Defendant were and are in violation of the Vernon's Missouri Stat. § 407.010, *et seq.*;

y. Montana: The aforementioned practices by Defendant were and are in violation of the Mont. Code § 30-14-101, *et seq.*;

z. Nebraska: The aforementioned practices by Defendant were and are in violation of the Neb. Code Ann. § 59-801, *et seq.*, and the Nebraska Consumer Protection Act, Neb. Rev. Stat. § 59-1601, *et seq.*;

aa. Nevada: The aforementioned practices by Defendant were and are in violation of the Nevada Unfair Trade Practices Act, Nev. Rev. Stat. § 598A.010, *et seq.*, and the Nevada Deceptive Trade Practices Act, Nev. Rev. Stat. § 598.0903, *et seq.*;

bb. New Hampshire: The aforementioned practices by Defendant were and are in violation of the N.H. Rev. Stat. § 358-A:1, *et seq.*;

cc. New Jersey: The aforementioned practices by Defendant were and are in violation of the New Jersey Antitrust Act, N.J. Stat. Ann. § 56:9-1, *et seq.*, and the New Jersey Consumer Fraud Act, N.J. Stat. Ann. § 56:8-1, *et seq.*;

dd. New Mexico: The aforementioned practices by Defendant were and are in violation of the New Mexico Antitrust Act, N.M. Stat. Ann. § 57-1-1, *et seq.*, and the New Mexico Unfair Practices Act, N.M. Stat. Ann. § 57-12-1, *et seq.*;

ee. New York: The aforementioned practices by Defendant were and are in violation of the Donnelly Act, N.Y. Gen. Bus. Law § 340, *et seq.*, and the New York Deceptive Acts and Practices Act, N.Y. Gen. Bus. Law § 349, *et seq.*;

ff. North Carolina: The aforementioned practices by Defendant were and are in violation of North Carolina's antitrust and unfair competition law, N.C. Gen. Stat. § 75-1, *et seq.*, and N.C. Gen. Stat § 75-1.1;

gg. North Dakota: The aforementioned practices by Defendant were and are in violation of the North Dakota Antitrust Act, N.D. Cent. Code § 51-08.1-01, *et seq.*, and the North Dakota Consumer Fraud Act, N.D. Cent. Code § 51-15-01, *et seq.*;

hh. Ohio: The aforementioned practices by Defendant were and are in violation of the Ohio Rev. Stat. § 1345.01, *et seq.*;

ii. Oklahoma: The aforementioned practices by Defendant were and are in violation of the Okla. Stat. 15 § 751, *et seq.*;

jj. Oregon: The aforementioned practices by Defendant were and are in violation of the Or. Rev. Stat § 646.605, *et seq.*;

kk. Pennsylvania: The aforementioned practices by Defendant were and are in violation of the 73 Pa. Stat. § 201-1, *et seq.*;

ll. Rhode Island: The aforementioned practices by Defendant were and are in violation of the R.I. Gen. Laws § 6-13.1-1, *et seq.*;

mm. South Carolina: The aforementioned practices by Defendant were and are in violation of the S.C. Code Laws § 39-5-10, *et seq.*;

nn. South Dakota: The aforementioned practices by Defendant were and are in violation of South Dakota's antitrust law, S.D. Codified Laws § 37-1-3, *et seq.*, and deceptive trade practices and consumer protection law, S.D. Codified Laws § 37-24-1, *et seq.*;

oo. Tennessee: The aforementioned practices by Defendant were and are in violation the Tennessee Trade Practices Act, Tenn. Code Ann. § 47-25-101, *et seq.*, and the Consumer Protection Act, Tenn. Code Ann. § 47-18-101, *et seq.*;

pp. Texas: The aforementioned practices by Defendant were and are in violation of the Tex. Bus. & Com. Code § 17-.41, *et seq.*;

qq. Utah: The aforementioned practices by Defendant were and are in violation of the Utah Code Ann. § 76-10-911, *et seq.*, and § 13-11-1, *et seq.*;

rr. Vermont: The aforementioned practices by Defendant were and are in violation of the Vt. Stat. Ann. 9, § 2453, and the Vermont Consumer Fraud Act, Ann. 9 Vt. § 2451, *et seq.*;

ss. Virginia: The aforementioned practices by Defendant were and are in violation of the Va. Code § 59.1-196, *et seq.*;

tt. Washington: The aforementioned practices by Defendant were and are in violation of the Wash. Rev. Code § 19.86.010, *et seq.*;

uu. West Virginia: The aforementioned practices by Defendant were and are in violation of the W. Va. Code § 47-18-1, *et seq.*, and the West Virginia Code § 46A-6-101, *et seq.*;

vv. Wisconsin: The aforementioned practices by Defendant were and are in violation of the Wisconsin Antitrust Act, Wis. Stat. § 133.01, *et seq.*, and the Wisconsin Unfair Trade Practices Act, Wis. Stat. § 100.20, *et seq.*

97. Plaintiff seeks damages, multiple damages, treble damages, and other damages as permitted by state law, for its injuries caused by these violations pursuant to these statutes.

98. Plaintiffs and the End-Payor Classes, also hereby seek a declaratory judgment that Defendant's conduct in seeking to prevent competition through the scheme set forth herein is unlawful. Plaintiff and the End-Payor Classes further seek equitable and injunctive relief to

correct for the anticompetitive market effects and other harms to purchasers caused by the unlawful conduct of Defendant, and other relief so as to assure that similar conduct does not occur in the future.

THIRD CAUSE OF ACTION

FOR RESTITUTION, DISGORGEMENT AND CONSTRUCTIVE TRUST FOR UNJUST ENRICHMENT BY DEFENDANT

99. Plaintiff repeats and realleges the preceding and subsequent paragraphs as though set forth herein.

100. Defendant has benefitted from the overcharges it has been able to levy for Arava, resulting from acts alleged in this Complaint, and resulting in overpayments by plaintiffs and the classes for Arava.

101. Plaintiffs and the members of the classes have conferred upon Defendant an economic benefit in the nature of revenues resulting from unlawful overcharges, to plaintiff's and the classes' economic detriment.

102. The economic benefit of overcharges obtained by supra-competitive prices is a direct and proximate cause of the Defendant's anticompetitive and unjust behavior restricting competition as set forth above.

103. The benefit held by the Defendant rightfully belongs to Plaintiff and the members of the classes, as Plaintiff and the members of the classes paid these anticompetitive and unjust sums to Defendant during the Class Period, when the Defendant used anticompetitive measures to block generic entry into the market.

104. Defendants to be permitted to retain any of the Plaintiff's and the members of the classes' overpayments for Arava derived from their unfair and unconscionable methods, acts and trade practices, including, but not limited to, the acts alleged herein that were designed to prevent introduction of generic bioequivalents to Arava into the United States market.

105. Plaintiffs and the members of the classes are entitled to a constructive trust over that portion of the additional profits they contributed to Defendant as a result of Defendant's illegal and unjust actions.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff prays that:

A. the Court determine that this action may be maintained as a class action pursuant to Rule 23(b)(2) of the Federal Rules of Civil Procedure with respect to Plaintiff's claims for declaratory, equitable and injunctive relief, and Rule 23(b)(3) and Rule 23(c)(4) of the Federal Rules of Civil Procedure with respect to the claims for liability; and declare the Plaintiff as the representative of the End-Payor Classes;

B. the conduct alleged herein be declared, adjudged and decreed to be in violation of Section 2 of the Sherman Act, of the statutes of the states set forth above, and the common law of unjust enrichment;

C. Plaintiff be awarded damages and, where applicable, treble, multiple, and other damages, according to the laws of the states, including interest;

D. Plaintiff recover in restitution the amounts by which Defendant has been unjustly enriched;

E. Defendant be enjoined from continuing the illegal and unjust activities alleged herein;

F. Plaintiff and the End-Payor Classes recover their costs of suit, including reasonable attorneys' fees and expenses as provided by law;

G. Plaintiff and the End-Payor Classes be granted such other and further as the Court deems just and necessary.

JURY DEMAND

Plaintiff demands a trial by jury, pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, of all issues so triable.

Dated: October 12, 2007

Respectfully Submitted,

/s/ Peter D. St. Phillip
Richard Cohen (RC-(5220)
Peter St. Phillip (PS-0726)
LOWEY DANNENBERG BEMPORAD
SELINGER & COHEN, P.C.
White Plains Plaza
One North Broadway
White Plains, NY 10601
Telephone: (914) 997-0500
Facsimile: (914) 997-0035

Thomas M. Sobol
David S. Nalven DN-2374
Edward Notargiacomo
HAGENS BERMAN SOBOL SHAPIRO LLP
One Main Street, Fourth Floor
Cambridge, MA 02142
Telephone: (617) 482-3700
Facsimile: (617) 482-3003

Mark M. Sandmann
Mark D. Fischer
Jeffrey Swann
RAWLINGS & ASSOCIATES, P.L.L.C.
325 W. Main Street
Louisville, KY 40202
Telephone: (502) 814-2157
Facsimile: (502) 584-8580

EXHIBIT A

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202.662.6000
FAX 202.662 6291
WWW COV COM

WASHINGTON
NEW YORK
SAN FRANCISCO
LONDON
BRUSSELS

PETER O. SAFIR
TEL 202.662 5162
FAX 202.778 5162
PSAFIR@COV.COM

March 31, 2005

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Aventis Pharmaceuticals Inc. a member of the sanofi-aventis Group (referred to as 'Aventis') submits this petition under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (21 U.S.C. § 355(j)), 21 C.F.R. §§ 314.94(a)(7), and 21 C.F.R. part 320 to request that the Commissioner of Food and Drugs refuse to approve abbreviated new drug applications ("ANDAs") referencing Arava® (leflunomide) tablets unless the applications (1) contain data from *in vivo* bioequivalence studies confirming that five of their proposed 20 mg leflunomide tablets are bioequivalent to one Arava® 100 mg tablet or (2) seek approval of 100 mg leflunomide tablets that are bioequivalent to 100 mg Arava® tablets.

A. Action Requested

Aventis requests that if an ANDA applicant is not seeking approval of a 100 mg leflunomide tablet that is bioequivalent to Arava® 100 mg tablets, that FDA require the applicant to perform *in vivo* bioequivalence testing to confirm that five of its 20 mg tablets are bioequivalent to one Arava® 100 mg tablet. Aventis further requests that the agency withhold final approval of any ANDA that (1) does not seek approval of a 100 mg leflunomide tablet that is bioequivalent to Arava® 100 mg or (2) does not establish *in vivo* bioequivalence between five 20 mg leflunomide tablets and one Arava® 100 mg tablet.

2005P-0127

CP1

B. Statement of Grounds

I. Background

Aventis holds the new drug application ("NDA") for Arava®.* Arava® is available in 10, 20, and 100 mg tablets. The 100 mg tablet is used for the loading dose that is recommended to initiate Arava® therapy. Specifically, as set forth in the Dosage and Administration section of the approved Arava® package insert ("PI"), [1]

> **Loading Dose**
> Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.

While the Arava® NDA was pending, HMR requested that the use of "5 X 20 mg tablets" be permitted as an alternative to the 100 mg tablet loading dose.[2] FDA denied this request, concluding that the comparative dissolution data was insufficient to support the approval of the alternative dosing regimen.[3] Further FDA stated that it would require a showing of bioequivalence in order to permit five 20 mg Arava® tablets to be used as an alternative to a single 100 mg tablet loading dose.[4]

II. Analysis

On information and belief, FDA has accepted a number of ANDAs seeking approval to market 10 and 20 mg -- but not 100 mg -- generic leflunomide tablets.[5] These applicants, unlike Aventis, would thus have no 100 mg tablet to

---

* A predecessor company, Hoechst Marion Roussel, Inc. ("HMR") was the NDA sponsor. Quintiles BRI was HMR's U.S. agent for NDA (No. 20-905).

[1] Package insert for Arava® Tablets (leflunomide). (Tab 1).

[2] NDA 20905, Clinical Pharmacology and Biopharmaceutics Review(s) 2. (Tab 2).

[3] Letter dated June 23, 1998, from Quintiles to Sandra Cook, Project Manager, Division of Anti-Inflammatory, Analgesic, and Opthalmologic Drug Products, FDA. (Tab 3).

[4] Facsimile Transmission dated August 6, 1998 from Sandra Cook at FDA to Joan Bates at Quintiles. (Tab 4).

[5] The analysis that follows does not apply to any ANDA seeking approval of a 100 mg leflunomide tablet that is bioequivalent to Arava® 100mg tablet. Sanofi-aventis does not object to such ANDAs on these grounds.

reference in either the "description," "absorption," or "dosing and administration" sections of their labeling. Aventis believes that these applicants are instead seeking to include a loading dose of five 20 mg leflunomide tablets or seeking to exclude the loading dose altogether. FDA has previously determined, however, that approval of such an alternative loading dose would require additional bioequivalence data not contained in the Arava® NDA. FDA thus cannot approve any ANDA for leflunomide not seeking approval of a 100 mg leflunomide tablet unless it contains *in vivo* bioequivalence data establishing that 5 of the proposed 20 mg leflunomide tablets are bioequivalent to a 100 mg Arava® tablet. Only then could the ANDA product bear the appropriate dosage and administration labeling information -- i.e., instructions to permit the use of five 20 mg tablets as an alternative to the 100 mg Arava® tablet loading dose.

Section 505(j)(2)(A)(v) of the FDCA provides that an ANDA must contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition . . . or because the new drug and the listed drugs are produced or distributed by different manufacturers." *See also* 21 CFR § 314.94(a)(8)(iv). Changes in labeling resulting from a difference in manufacturers, however, must not render the proposed generic less safe or effective than the listed drug for the remaining conditions of use. 21 CFR § 314.127(a)(7); *see also* Draft Guidance for Industry: Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications, lines 146-154 (Oct. 2000).

As discussed above, here, the labeling of the reference drug, Arava®, contains important dosage and administration information regarding a 100 mg loading dose. Leflunomide ANDAs must likewise contain such labeling. 21 U.S.C. § 355(j)(2)(A)(v); 21 § CFR 314.94(a)(8)(iv). This information is not the type of information that can be omitted from ANDA labeling simply because the reference drug and the ANDA drug are "produced or distributed by different manufacturers" and the ANDA manufacturer does not make a 100 mg tablet. 21 CFR § 314.127(a)(7).

Rather, omission of the loading dose information may render the generics less effective than Arava®, thereby making the ANDAs unapprovable; the ANDAs would be without the necessary evidence basis to provide for and match the labeling of Arava®. 21 CFR 314.127(a)(7) (ANDA approvable if labeling differences resulting from difference in manufacturer "do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."). Indeed, the three day 100 mg loading dose "is needed to provide steady-state concentration more rapidly" in patients first initiating leflunomide therapy. Although the Arava® PI explains, "[e]limination of the loading dose regimen may decrease the risk of adverse events which may be especially important for some patients at an increased risk of hematologic or hepatic toxicity . . . .;" the three day 100 mg loading dose "is needed to provide steady-state concentration more rapidly" in patients first initiating leflunomide therapy. The Arava® PI explains, "[w]ithout a loading dose, it is

estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that M1 plasma levels are dose proportional."

The importance of the rapid attainment of steady state plasma levels is supported in the Rheumatoid Arthritis (RA) treatment literature. DMARDs such as Arava should be introduced as soon as possible for the treatment of RA as recommended by treatment guidelines such as "American College of Rheumatology Subcommittee on RA Guidelines, 2002"[6] or the "Management of Early Rheumatoid, A National Clinical Guideline - Scottish Intercollegiate Guidelines Network, 2000."[7]

That erosive changes occur early in the disease, often in the first year,[8] also highlights the importance of an early therapeutic intervention. The initiation of DMARD therapy should not be delayed beyond 3 months for any patient with an established diagnosis who, despite adequate treatment with NSAIDs, has ongoing joint pain, significant morning stiffness or fatigue, active synovitis, persistent elevation of the ESR or CRP level, or radiographic joint damage (Tab 5). Even a brief delay, as little as 8-9 months, in starting DMARD therapy has a significant impact on disease parameters years later.[9,10] Additionally, mortality among RA patients who present early is lower when compared to RA patients who present late in their course of the disease.[11] In consequence, RA should be treated aggressively, as early as possible. Such an approach was proven to be better than the stepwise approach of carefully introducing consecutive

---

[6] Guidelines for the Management of Rheumatoid Arthritis. 2002 Update. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Arthritis & Rheum. 2002;46:328-346. (Tab 5).

[7] Management of Early Rheumatoid Arthritis. A National Clinical Guideline. Scottish Intercollegiate Guideline Network. December 2000. (Tab 6).

[8] McGonagle D, Green MJ, Proudman S, Richardson C, Veale D, O'Connor P et al. The majority of patients with rheumatoid arthritis have erosive disease at presentation when magnetic resonance imaging of the dominant hand is employed. Br. J. Rheumatol. 1997;36(Suppl):230. (Tab 7).

[9] Egsmose C, Lund B, Borg G, Petterson H, Berg E, Brodin U, et al. Patients with rheumatoid arthritis benefit from early 2nd line therapy: 5-year followup of a prospective double blind placebo controlled study. J. Rheumatol. 1995;22:2208-13. (Tab 8).

[10] Tsakonas E. Fitzgerald AA, Fitzcharles MA, Vividino A, Thorne JC, M'Seffar A, et al. Consequences of the delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. J. Rheumatol. 2000;27:623-9. (Tab 9).

[11] Symmons DPM, Jones MA, Scott DL, Prior P. Longterm mortality outcome in patients with rheumatoid arthritis: early presenters continue to do well. J. Rheumatol. 1998;25:1072-7. (Tab 10).

DMARDs of increasing potential.[12,13] The general, joint-protecting effect of initiation of intensive, first-line treatment as soon as diagnosis is established was again recently demonstrated in Landewe 2002.[14]

Clinical trials conducted with leflunomide similarly indicated that insufficient treatment already results in significantly more joint damage and irreversible deterioration in physical function after 4 and 6 months, respectively, as evidenced by disease progression in the placebo groups in leflunomide studies US301 and MN301.[15,16,17]

It is consequently important to initiate Arava therapy with a loading dose of one 100 mg tablet per day for 3 days in order to provide steady state concentrations more rapidly and prevent as much as possible a delay in the establishment of an efficient treatment with all the risks associated with this delay.

Leflunomide ANDAs thus cannot be permitted to omit the loading dose information. Nor can ANDAs be permitted to simply substitute "five 20 mg tablets" for the reference to "one 100 mg tablet" in the loading dose section. During its review of the Arava® NDA, FDA determined that additional data would be required to support such alternative dosing information. Accordingly, in order for a generic to obtain approval of a "5 X 20 mg tablet" loading dose in place of the single 100 mg tablet dose,

---

[12] Van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ et al. The Effectiveness of Early Treatment with "Second-Line" Antirheumatic Drugs: a Randomized, Controlled Trial. Ann. Intern. Med. 1996;124:699-707. (Tab 11).

[13] Van Jaarsveld CH, Jacobs JW, van der Veen MJ, Blaauw AA, Kruize AA, Hofman DM et al, on behalf of the Rheumatic Research Foundation Utrecht, The Netherlands. Aggressive treatment in early rheumatoid arthritis: a randomised controlled trial. Ann. Rheum. Dis. 2000;59:468-77. (Tab 12).

[14] Landewé RB, Boers M, Verhoeven AC, Westhovens R, van de Laar MA, Markusse HM, et al. COBRA Combination Therapy in Patients with Early Rheumatoid Arthritis: Long-Term Structural Benefits of a Brief Intervention. Arthritis Rheum 2002;46(2):347-356. (Tab 13).

[15] Smolen JS, Kalden JR, Scott DL, Rozman B, Kvien TK, Larsen A, Loew-Friedrich I, Oed C, Rosenburg R, and the European Leflunomide Study group. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. The Lancet 1999;353:259-266. (Tab 14).

[16] Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, Fox R, Moreland L, Olsen N, Furst D, Caldwell J, Kaine J, Sharp J, Hurley F, Loew-Friedrich I, for the Leflunomide Rheumatoid Arthritis Investigators group. Treatment of Active Rheumatoid Arthritis With Leflunomide Compared With Placebo and Methotrexate. Arch. Intern. Med. 1999;159:2542-2550. (Tab 15).

[17] Strand V. Counterpoint from the trenches: a pragmatic approach to therapeutic trials in rheumatoid arthritis. Arthritis & Rheumatism 2004. (Tab 16).

the applicant must submit data establishing *in vivo* bioequivalence between five of its 20 mg tablets and a single Arava® 100 mg tablet. Without such data an ANDA seeking to substitute a loading dose of five 20 mg tablets would not be approvable. Only with *in vivo* bioequivalence data can a "5 X 20 mg tablets" loading dose be a labeled alternative to the approved Arava® 100 mg tablet loading dose.

III. Conclusion

Aventis respectfully submits that FDA must take the actions requested in this petition to ensure that leflunomide ANDAs contain proper labeling for the safe and effective administration of the drug. Specifically, to ensure that new patients are not put at risk when initiating leflunomide therapy, FDA should not approve a leflunomide ANDA unless (1) it seeks approval of a 100 mg tablet that is bioequivalent to the Arava 100mg loading dose or (2) it contains data establishing *in vivo* bioequivalence between five 20 mg leflunomide tablets and the Arava 100 mg tablet.

C. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 & 25.31.

D. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Peter O. Safir
Kelly A. Falconer
COVINGTON & BURLING
1201 Pennsylvania Avenue, N.W.
P.O. Box 7566
Washington, D.C. 20004-2401
(202) 662-6000

Counsel for Aventis

INDEX TO FOOTNOTES **Number**

EXHIBIT B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 13 2005

4842 5 SEP 16 A9:39

Peter O. Safir, Esq.
Covington & Burling
1201 Pennsylvania Avenue, NW
Washington, D.C. 20004-2401

Re: Docket No. 2005P-0127/CP1

Dear Mr. Safir:

This responds to your citizen petition dated March 31, 2005 (Petition), and your related comment dated June 10, 2005 (Comment), both submitted on behalf of Aventis Pharmaceuticals Inc. (Aventis), concerning the approval of abbreviated new drug applications (ANDAs) for leflunomide. Aventis holds the new drug application (NDA 20-905) for the reference listed drug (RLD) for leflunomide, which is marketed under the brand name Arava. Arava is commercially available in 10-milligram (mg) and 20-mg strengths. Aventis also distributes 100-mg tablets, not available in pharmacies, but available free to physicians in blister packs of three tablets.

In the Petition, you request that (1) if an ANDA applicant is not seeking approval of a 100-mg leflunomide tablet that is bioequivalent to Arava 100-mg tablets, the Food and Drug Administration (FDA or the Agency) require the applicant to perform in vivo bioequivalence testing to confirm that five of its 20-mg tablets are bioequivalent to one Arava 100-mg tablet, and (2) the Agency withhold final approval of any leflunomide ANDA that either (a) does not seek approval of a 100-mg leflunomide tablet that is bioequivalent to Arava 100-mg tablets or (b) does not establish in vivo bioequivalence between five 20-mg leflunomide tablets and one Arava 100-mg tablet.

For the reasons that follow, the Petition is denied. This decision is based on a review of the Petition and the comments submitted in response to it,[1] as well as other information available to the Agency. Generic leflunomide product lines that provide the 10-mg and/or 20-mg strengths that contain the same labeling as Arava are not compelled to also provide the 100-mg tablet. Moreover, a generic sponsor of a 20-mg leflunomide tablet who has demonstrated bioequivalence to Arava 20-mg tablets, is not also required to demonstrate bioequivalence of five of the 20-mg generic leflunomide product to one Arava 100-mg tablet.

[1] These include comments submitted by Kali Laboratories, Inc. (Kali), dated May 12, 2005 (2005P-0127/C1), comments submitted by Olsson, Frank and Weeda, P.C., dated May 18, 2005 (2005P-0127/C2), and your Comment referenced above (2005P-0127/RC1).

2005P-0127

PDN 1

Docket No. 2005P-0127/CP1

I. BACKGROUND

A. Factual Information

Leflunomide (Arava) is a pyridimine synthesis inhibitor that is indicated in adults for the treatment of active rheumatoid arthritis (RA) to reduce signs and symptoms and to retard structural damage. Leflunomide is metabolized to one primary active metabolite (M1) that is responsible for essentially all of its in vivo activity. M1 is eliminated by further metabolism and subsequent renal excretion as well as by direct biliary excretion. M1 has a half-life of 15 days. The usual daily dose of leflunomide is 20 mg. Because of the long half-life of M1, however, a loading dose of 100 mg per day for 3 days is recommended in Arava's approved labeling to quickly reach steady state plasma concentrations of M1. The use of a loading dose is not essential to the effective use of the product, and elimination of the loading dose may decrease the risk of adverse events.[2]

Bioequivalence between five 20-mg tablets and one 100-mg tablet of Arava has not been established. Arava 100-mg tablets have a formulation that is not proportionally similar relative to either the 20-mg or the 10-mg tablets.[3] FDA's publication *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly referred to as the Orange Book) lists both the 20-mg and the 100-mg tablets of Arava as the reference listed drugs (RLDs) for leflunomide tablets. FDA would not waive the requirement for the submission of evidence measuring the in vivo bioequivalence of five 20-mg leflunomide tablets (or ten 10-

---

[2] The *DOSAGE AND ADMINISTRATION* portion of Arava's labeling states in part the following:

> **Loading Dose**
> Due to the long half-life in patients with RA and recommended dosing interval (24 hours), a loading dose is needed to provide steady-state concentrations more rapidly. It is recommended that ARAVA therapy be initiated with a loading dose of one 100 mg tablet per day for 3 days.
> Elimination of the loading dose regimen may decrease the risk of adverse events. This could be especially important for patients at increased risk of hematologic or hepatic toxicity, such as those receiving concomitant treatment with methotrexate or other immunosuppressive agents or on such medications in the recent past (see **WARNINGS — Hepatotoxicity**).

Loading dose is also referred to in the following portion of the labeling:

> **Absorption**
> Following oral administration, peak levels of the active metabolite, M1, occurred between 6 - 12 hours after dosing. Due to the very long half-life of M1 (~2 weeks), a loading dose of 100 mg for 3 days was used in clinical studies to facilitate the rapid attainment of steady-state levels of M1. Without a loading dose, it is estimated that attainment of steady-state plasma concentrations would require nearly two months of dosing. The resulting plasma concentrations following both loading doses and continued clinical dosing indicate that M1 plasma levels are dose proportional.

[3] The 20-mg and 10-mg tablets are proportionally similar (see NDA 20905, Clinical Pharmacology and Biopharmaceutics Review(s) (attached at Tab 2 to the Petition) at 3). The 100-mg and 20-mg tablets are not proportionally similar (see Leflunomide Tablets, NDA Amendment/Biopharmaceutical Information, NDA #20-[90]5, enclosed with letter dated June 23, 1998, from Quintiles to Sandra Cook, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products, FDA (attached at Tab 3 to the Petition) at 10). For a detailed definition of *dose proportionality*, see p. 11 of the guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations*. Proportionality and nonproportionality of dosage strengths are important when considering bioequivalence requirements (e.g., when granting waivers of in vivo bioequivalence studies for a lower strength or strengths of a drug product).

mg tablets) and a 100-mg tablet if an ANDA applicant proposed to recommend using five 20-mg tablets (or ten 10-mg tablets) instead of a 100-mg tablet for the loading dose.

Arava was approved on September 10, 1998, at 10-mg, 20-mg, and 100-mg strengths.[4] As a new chemical entity, Arava had 5-year exclusivity under section 505(j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355 (j)(5)(F)(ii)), during which time no generic applications could be submitted.[5] Because FDA determined under section 505A of the Act that Arava was entitled to pediatric exclusivity, the period of exclusive marketing was extended 6 months (i.e., until March 10, 2004).[6]

In January 2002, in a letter to pharmaceutical buyers, Aventis announced its decision "to discontinue [the] 100 mg Arava® (leflunomide) tablets trade package."[7] As your Comment acknowledges, Aventis no longer *sells* the 100-mg strength of the product (Comment at 2). Aventis does, however, continue to make the 100-mg product available free to physicians (*Id.*).[8] As acknowledged in comments submitted to the docket, generic drug applicants seek approval of the 10-mg and 20-mg strengths of leflunomide.

---

[4] In 2002, in a citizen petition, Public Citizen asked the Agency to remove Arava from the market, based on the claim that its adverse events compared unfavorably with older treatments for rheumatoid arthritis. In 2003, an advisory committee meeting was held to consider the safety of the product. On March 23, 2004, in a formal response to the 2002 citizen petition, FDA announced that it continues to regard the product as safe (see Docket No. 2002P-0139/CP1).

[5] Arava also had 5-year exclusivity under section 505(c)(3)(E)(ii) of the Act. The Act's 5-year exclusivity provisions state that no ANDA (or new drug application under section 505(b)(2) of the Act (505(b)(2) application)) that references an NDA with such exclusivity can be submitted to FDA for 5 years after the date of approval of the NDA, except that an ANDA (or 505(b)(2) application) can be submitted 4 years after the date of the NDA's approval if it contains a certification stating that one or more patents claiming the drug described in the NDA, or use thereof, is invalid or not infringed (a paragraph IV certification) (see sections 505(j)(5)(F)(ii) and 505(c)(3)(E)(ii) of the Act). Such patents are listed in the Orange Book. Although a patent had been previously listed in the Orange Book for Arava, no patents were listed for Arava on or after the fourth anniversary of its approval, and no paragraph IV certifications were submitted in any ANDA for a generic leflunomide product. Accordingly, Arava enjoyed the full 5-year period of marketing exclusivity afforded by sections 505(j)(5)(F)(ii) and 505(c)(3)(E)(ii) of the Act.

[6] Your Petition was submitted approximately one year after this date. One commenter notes (see 2005P-0127/C1 at 1) that this would be at the end of the normal ANDA review cycle for an ANDA submitted on or near the date ANDAs were first eligible for submission, suggesting that the Petition intends (at least in part) to delay generic competition. We also note that the majority of the citations in your Petition are many years old, and were available to Aventis well before the petition was submitted.

[7] See http://www.aventis.custservices.com/news.asp?up=103. For a brief time FDA listed the 100-mg Arava product in the *Discontinued Drug Product List* of the Orange Book, but it is now listed again in the Orange Book's main *Prescription Drug Product List*.

[8] See also http://www.arava.com/professional/about_arava/initiation.do?warning=1.

B. Relevant Statutory Background

1. Summary of Approval Process

Under the Act, sponsors seeking to market innovator drugs must first obtain FDA approval by filing an NDA. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug (see sections 505(a) and (b) of the Act). The NDA applicant is also required to submit certain patent information to FDA; the Agency publishes patent information for approved drugs in the Orange Book.

The Act permits applicants to submit ANDAs for approval of generic versions of approved drug products (see section 505(j) of the Act). The ANDA process shortens the time and effort needed for approval by, among other things, allowing the applicant to demonstrate that its drug product is bioequivalent to the innovator drug, rather than reproduce the safety and effectiveness data for the innovator drug (see *Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990)). The timing of approval of an ANDA depends in part on statutory patent listing, patent certification, and exclusivity protections added to the Act by the 1984 Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments), Pub. L. No. 98-417, 98 Stat. 1585. As mentioned above, by operation of the exclusivity protections afforded under the Act, ANDAs for leflunomide were not eligible for submission until March 10, 2004.

2. Summary of Statutory and Regulatory Standards

The Act generally requires an ANDA applicant to provide, among other things, information to show that the generic drug is bioequivalent[9] to the RLD (see 21 U.S.C. 355(j)(2)(A)(iv)). When there are multiple strengths of a product, this refers to bioequivalence between the same strength of the ANDA product and the RLD.[10,11] There is no requirement for an ANDA sponsor to

---

[9] Section 505(j)(8)(B) of the Act provides that a generic drug shall be considered to be bioequivalent to the listed drug if:

> (i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or (ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

[10] The preamble to our 1992 final rule on ANDAs explains that, "In some instances, such as the submission of an ANDA for a product with multiple strengths, there may be more than one reference listed drug. In these instances, FDA considers each strength to represent a different drug product and will require an ANDA applicant to demonstrate that each proposed drug product is bioequivalent to its corresponding reference listed drug" (*Abbreviated New Drug Application Regulations*; Final Rule, 57 FR 17950, April 28, 1992).

[11] Often the showing of bioequivalence can be accomplished without the submission of an in vivo study. FDA's regulations describe when FDA may waive in vivo bioequivalence studies on different strengths of a drug in the same dosage form:

> The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the conditions in paragraphs (d)(2)(i) through (d)(2)(iii) of this section are met:

demonstrate equivalence between different strengths of its own product line.[12] Assuming that the other requirements applicable to ANDAs (which are not at issue here) are satisfied, FDA must approve the ANDA unless the information submitted in the ANDA is insufficient to show that the generic drug is bioequivalent to the RLD (see 21 U.S.C. 355(j)(4)(F)).

The Act also requires an ANDA applicant to provide, among other things, information to show that the labeling proposed for the generic drug is the same as the labeling approved for the RLD, except for changes required because of differences approved under an ANDA suitability petition or because the generic drug and the RLD are produced or distributed by different manufacturers (see 21 U.S.C. 355(j)(2)(A)(v)). Examples of these changes are listed at 21 CFR 314.94(a)(8)(iv), although this list is not exhaustive.[13] Differences in labeling that may result because a generic drug and the RLD are produced or distributed by different manufacturers include, but are not limited to, differences in the labeled name, address, and phone number for the drug manufacturer; differences in labeled colors; differences in the labeled indications for the drug (e.g., if the RLD had existing exclusivity for a particular indication); and differences in the drug's labeled strengths (e.g., if a generic manufacturer does not seek approval for all strengths approved for the RLD) (this point is discussed further in section II below).

II. DISCUSSION

You believe that FDA has accepted ANDAs seeking to market 10-mg and 20-mg tablets but not 100-mg tablets of leflunomide. You claim that the products described in these ANDAs would have no 100-mg tablets to refer to in their labeling (Petition at 2). You maintain that the approved labeling for Arava contains important dosage and administration information regarding a 100-mg loading dose and that leflunomide ANDAs must likewise contain such labeling (Petition at 4-5). You assert that this information is not the type of information that can be omitted from ANDA labeling simply because the reference drug and the ANDA drug are

---

(i) The bioavailability of this other drug product has been measured;
(ii) Both drug products meet an appropriate in vitro test approved by FDA; and
(iii) The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients.

(21 CFR 320.22(d)(2)).

[12] Both the Act and the bioequivalence regulations (see 21 CFR Part 320) refer only to bioequivalence between the subject of the ANDA and the RLD.

[13] See, e.g., February 15, 2002, response to Donald O. Beers, David E. Korn, William J. McNichol, Marc J. Scheineson, and Tracy Zurzolo Frisch regarding Docket Nos. 00P-1550/CP1 & PSA1 and 01P-0428/CP1 & PSA1 concerning generic cefuroxime axetil products, at 18 ("The plain language of § 314.94(a)(8)(iv) explicitly recognizes that these differences listed in the regulation are examples; therefore, § 314.94(a)(8)(iv) recognizes that there are other differences in labeling between generic drug products and reference listed drugs that are permissible due to the fact that the generic drug product and reference listed drug product are produced or distributed by different manufacturers").

produced or distributed by different manufacturers and the ANDA manufacturer does not make a 100-mg tablet (Petition at 3 and Comment at 3). Finally, you claim that omission of the loading dose information may render the generics less effective than Arava (Petition at 3 and Comment at 3).

Your argument seems to be based on a false premise, namely, that if a particular generic manufacturer recommends in leflunomide labeling a loading dose of 100 mg for three days (3 x 100 mg), the manufacturer either must (1) provide its own 100-mg product or (2) recommend using five of its 20-mg tablets. You incorrectly speculate that generic sponsors will attempt to either replace the 100-mg tablet loading dose with a loading dose of five 20-mg tablets or remove mention of the loading dose from the label (Petition at 3). In the rest of the Petition, as well as in your Comment, you argue that replacing the 100-mg loading dose with a loading dose of five 20-mg tablets should require an in vivo bioequivalence study, and that it is legally and medically inappropriate to remove mention of the loading dose from the label. You seem to ignore a third possibility: that the labeling for a generic leflunomide product can recommend a loading dose of 3 x 100 mg that can be accomplished by the use of an approved 100-mg tablet from a different manufacturer. Given the unusual manner in which the 100-mg tablet for the loading dose has been distributed by Aventis (i.e., in blister packs of 3, for free and only to, and at the request of, a physician) and the fact there are circumstances when a loading dose should perhaps not be used, we do not find it unreasonable for a generic manufacturer to elect to market only the other dosage strengths.

A generic sponsor that markets only 20-mg and 10-mg leflunomide tablets must have the same labeling as the RLD, except for differences that would be permitted under 21 U.S.C. 355(j)(2)(A)(v), discussed in subsection I.B.2 above. As does the approved labeling for Arava (see footnote 2, *supra*), approved labeling for generic leflunomide products would include the recommendation of using 100-mg tablets for the loading dose. The 100-mg tablets could be either 100-mg Arava tablets or 100-mg generic tablets from a different sponsor that have been demonstrated to be bioequivalent to the 100-mg Arava tablets.[14] We agree that changes in labeling resulting from a difference in manufacturers must not render the proposed generic drug product less safe or effective than the RLD. But we do not see this as an issue here, for we do not intend to permit the labeling regarding use of a 100-mg tablet for the loading dose to be omitted, as you surmise (see Petition at 3 and 5); nor do we see that any change not permitted by the Act is needed in this labeling if a generic manufacturer chooses to market only the 20-mg and 10-mg strengths of leflunomide.

Labeling for generic leflunomide products approved in 10- and 20-mg strengths may reference a 100-mg leflunomide tablet that the generic sponsor does not produce. As reflected by existing precedents, ANDA sponsors may refer in their labeling to products they do not manufacture. For example, the product labeling for the anti-retroviral drug Videx (didanosine) delayed-release capsules makes reference to the package inserts for Videx chewable/dispersible tablets and

[14] Your Comment acknowledges that an ANDA applicant that seeks approval of a 20-mg leflunomide tablet, but not a 100-mg tablet, could propose to "reference [in the drug's label] a 100 mg tablet that the generic does not manufacture" (Comment at 3). You go on to assert that this option should not be permitted (*Id.*); however, you provide no explanation for your assertion, and, for the reasons discussed in the text above, we see no reasoned basis to accept it.

Videx pediatric powder for oral solution for information regarding the pediatric dose. Currently, the only approved generic didanosine (Barr ANDA 77-167) is for a delayed-release capsule, which has labeling that makes reference to the other Videx dosage forms, even though Barr does not itself provide these other dosage forms. It is also not uncommon for brand name products to refer in their labeling to other drugs that are not provided by the sponsor of the brand name product (e.g., the labeling of Oncaspar, an Aventis product, recommends its use in combination with the following products not made by Aventis: vincristine, methotrexate, cytarabine, daunorubicin, and doxorubicin; also, the labeling of Eloxatin, owned by Sanofi-Synthelabo, Inc., recommends that it be used in combination with infusional 5-FU/LV[5-fluorouracil/leucovorin], which Sanofi-Synthelabo, Inc., does not supply).

Additionally, there is nothing in the Act or the regulations that requires an ANDA applicant to seek approval for all available strengths of the RLD. Both the Act and the regulations state that the generic product must be the same strength (singular) as the listed drug (see 21 U.S.C. 355(j)(2)(A)(iii) and 21 CFR 314.92 and 314.94(a)(6)(i)), implying that each strength of a reference product is in some regards a separate listed drug (see footnote 10, *supra*). It is not unusual for an ANDA applicant to decline to seek approval for certain strengths approved for the RLD (see the June 11, 2002, response in Docket Nos. 01P-0495, 02P-0191, and 02P-0252, in which FDA permitted ANDAs for tramadol that do not provide a low dose for titration that is provided by the manufacturer of the RLD). The following products are all examples from the Orange Book (2004 printed edition) in which at least one generic manufacturer has omitted at least one strength of the RLD: alprazolam tablets, amitriptyline hydrochloride tablets, haloperidol tablets, hydralazine hydrochloride tablets, hydrochlorothiazide tablets, meclizine hydrochloride tablets, mirtazapine orally disintegrating tablets, nefazadone hydrochloride tablets, nifedipine capsules, nitrofurantoin (macrocrystaline) capsules, propranolol hydrochloride tablets, trazadone hydrochloride tablets, and thioridazine hydrochloride tablets.[15] It should be noted that the reverse may also be true (i.e., the reference product may not provide strengths that a generic applicant provides (e.g., methyldopa tablets, propranolol hydrochloride tablets)).

In light of the discussion above, FDA will require the labeling for generic leflunomide products to include the labeling approved for the RLD, Arava, concerning the use of a 100-mg loading dose. Thus, your concern that (1) this labeling will be omitted for generic leflunomide products that are approved at only 10-mg and 20-mg strengths, or (2) the labeling will be changed to recommend the use of five 20-mg tablets instead of a 100-mg tablet absent appropriate bioequivalence data, is unfounded.

---

[15] You state in your Comment that another example cited by Kali in its comments on the Petition (2005P-0127/C1), oxycodone hydrochloride extended release (ER) tablets, "is inapposite" because dose proportionality and/or bioavailability were established for each strength of the RLD (Comment at 3). You note that, in the case of leflunomide, dose proportionality has not been established for all of the RLD's approved strengths (*Id.*). However, while, as you acknowledge, the labeling for the generic oxycodone hydrochloride ER product includes (as does the labeling for its RLD) a statement asserting that dose proportionality and/or bioavailability have been established for all available strengths at which the RLD is approved, there is no such claim in the approved labeling for Arava. Therefore, an applicant seeking approval for generic leflunomide tablets need not establish dose proportionality for all of Arava's approved strengths; nor, as explained above, must it demonstrate bioequivalence of five 20-mg generic leflunomide tablets (or ten 10-mg tablets) to one Arava 100-mg tablet.

III. CONCLUSION

It is not necessary for a generic leflunomide sponsor to either produce a 100-mg tablet or demonstrate bioequivalence of five 20-mg tablets to one 100-mg Arava tablet. A generic leflunomide product that refers in its labeling to a 100-mg tablet (which is available from Aventis) as the loading dose will be appropriately labeled with respect to the loading dose. For these reasons your Petition is denied.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research